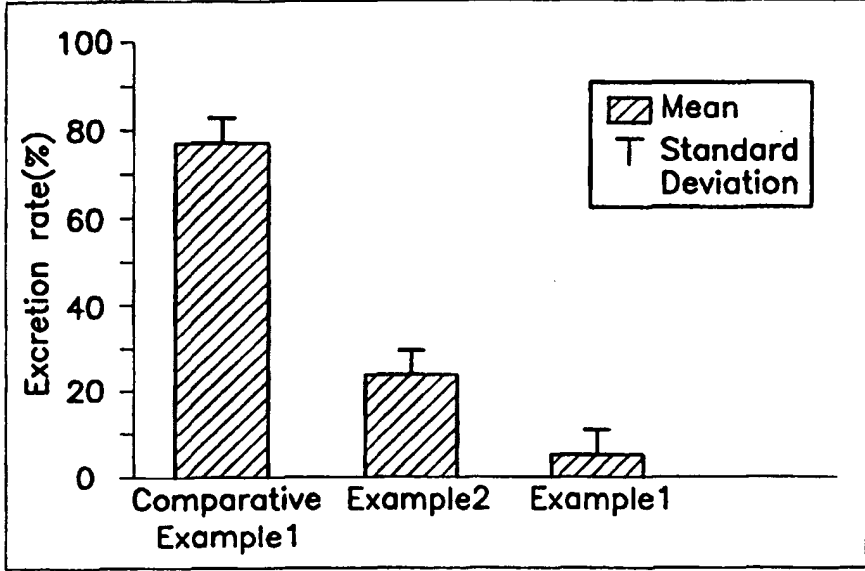




INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁷ : A61K 9/14, 47/44, 38/13, 47/30	A1	(11) International Publication Number: WO 00/40220 (43) International Publication Date: 13 July 2000 (13.07.00)												
<p>(21) International Application Number: PCT/KR99/00025</p> <p>(22) International Filing Date: 6 January 1999 (06.01.99)</p> <p>(71) Applicant (for all designated States except US): KOREA RESEARCH INSTITUTE OF CHEMICAL TECHNOLOGY [KR/KR]; 100, Jang-dong, Yuseong-ku, Daejeon-city 305-343 (KR).</p> <p>(72) Inventors; and (75) Inventors/Applicants (for US only): YUK, Soon-Hong [KR/KR]; Hanbit Apt., 133-1105, Eoeun-dong, 99, Yuseong-ku, Daejeon-city 305-333 (KR). CHO, Sun-Hang [KR/KR]; Hanwool Apt., 111-404, Shin-seong-dong 1-block, Yuseong-ku, Daejeon-city 305-345 (KR). LEE, Hai-Bang [KR/KR]; Hyundai Apt., 103-901, Doryong-dong, 431 Yuseong-ku, Daejeon-city 305-340 (KR).</p> <p>(74) Agent: KIM, Won-Ho; 702, Teheran Building, 825-33 Yok-sam-dong, Kangnam-ku, Seoul 135-080 (KR).</p>		<p>(81) Designated States: JP, US, European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).</p> <p>Published With international search report.</p>												
(54) Title: METHOD OF PREPARING PHARMACEUTICAL ACTIVE INGREDIENT COMPRISING WATER-INSOLUBLE DRUG AND PHARMACEUTICAL COMPOSITION FOR ORAL ADMINISTRATION COMPRISING THE SAME														
 <table border="1"><thead><tr><th>Example</th><th>Mean Excretion rate(%)</th><th>Standard Deviation (%)</th></tr></thead><tbody><tr><td>Comparative Example 1</td><td>~78</td><td>~5</td></tr><tr><td>Example 2</td><td>~25</td><td>~5</td></tr><tr><td>Example 1</td><td>~5</td><td>~5</td></tr></tbody></table>			Example	Mean Excretion rate(%)	Standard Deviation (%)	Comparative Example 1	~78	~5	Example 2	~25	~5	Example 1	~5	~5
Example	Mean Excretion rate(%)	Standard Deviation (%)												
Comparative Example 1	~78	~5												
Example 2	~25	~5												
Example 1	~5	~5												
<p>(57) Abstract</p> <p>A method of preparing a pharmaceutical active ingredient comprising a water-insoluble drug is provided. In the method, a water-insoluble drug in an organic solvent is mixed with a water-soluble polymer in an aqueous solvent and spray-dried. Thereafter, the drug microparticles is mixed with oil. The method can easily prepare a pharmaceutical active ingredient including water-insoluble drug, exhibiting good bioavailability. Accordingly, it is not required for specific technology in the preparation.</p>														

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece	ML	Mali	TR	Turkey
BG	Bulgaria	HU	Hungary	MN	Mongolia	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MR	Mauritania	UA	Ukraine
BR	Brazil	IL	Israel	MW	Malawi	UG	Uganda
BY	Belarus	IS	Iceland	MX	Mexico	US	United States of America
CA	Canada	IT	Italy	NE	Niger	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NL	Netherlands	VN	Viet Nam
CG	Congo	KE	Kenya	NO	Norway	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NZ	New Zealand	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	PL	Poland		
CM	Cameroon	KR	Republic of Korea	PT	Portugal		
CN	China	KZ	Kazakhstan	RO	Romania		
CU	Cuba	LC	Saint Lucia	RU	Russian Federation		
CZ	Czech Republic	LI	Liechtenstein	SD	Sudan		
DE	Germany	LK	Sri Lanka	SE	Sweden		
DK	Denmark	LR	Liberia	SG	Singapore		
EE	Estonia						

**METHOD OF PREPARING PHARMACEUTICAL ACTIVE INGREDIENT
COMPRISING WATER-INSOLUBLE DRUG AND PHARMACEUTICAL
COMPOSITION FOR ORAL ADMINISTRATION COMPRISING THE SAME**

5

BACKGROUND OF THE INVENTION

(a) Field of the Invention

The present invention relates to method of preparing a pharmaceutical active ingredient comprising water-insoluble drug and a pharmaceutical composition for oral administration comprising the same and, more particularly,
10 to a method of preparing a pharmaceutical active ingredient comprising the water-insoluble improved bioavailability with simple process.

(b) Description of the Related Art

When a water-insoluble drug is orally administrated into a patient,
15 bioavailability is low. Due to the low bioavailability, it is impossible to orally administrate the water-insoluble drug or for increasing the effective concentration of the drug in the blood, the patient frequently takes the water-insoluble drug for a long time. For example, the patient takes the water-insoluble drug three times a day for a week.

20 For improving bioavailability, studies to use oil and a surfactant has been attracted. Korean Patent Laid-open No. 96-21056 discloses that a drug is micro-emulsified by using oil and a surfactant. Furthermore, a drug is dissolved in an organic solvent and the mixture is micro-emulsified by using oil and a surfactant (Sandoz company, Swiss).

25 In addition, Korean Patent Laid-open No. 96-5136 discloses that drug in

alcohol such as ethanol or isopropanol or acetone is mixed with excess water under the condition of forming hydrosol and dried by rotary drying or freeze-drying to make preparation.

However, in the methods of Korean Patent Laid-open No. 96-21056 and
5 Sandoz company, the surfactant used hurts gastrointestinal tract. Furthermore, the method of Korean Patent Publication No. 96-5136 has disadvantages in that manufacturing process is complicate and it is required specific manufacturing technology.

10

SUMMARY OF THE INVENTION

It is an object of the present invention to provide a method of preparing a pharmaceutical active ingredient comprising a water-insoluble drug with simple and economical process.

It is another object of the present invention to provide a pharmaceutical
15 composition for oral administration comprising the water-insoluble drug.

These and other objects may be achieved by a method of preparing a pharmaceutical active ingredient comprising a water-insoluble drug. The method includes the steps of mixing a water-insoluble drug in an organic solvent with a water-soluble polymer in an aqueous solvent and spray-drying
20 the mixture.

Furthermore, the present invention provides the pharmaceutical composition for oral administration including a pharmaceutical active ingredient including water-insoluble drug microparticles combined with a water-soluble polymer.

BRIEF DESCRIPTION OF THE DRAWINGS

A more complete appreciation of the invention, and many of the attendant advantages thereof, will be readily apparent as the same becomes better understood by reference to the following detailed description when
5 considered in conjunction with the accompanying drawing, wherein:

FIG. 1 is a graph showing water-insoluble drug excretion rate after pharmaceutical compositions including pharmaceutical active ingredients of examples 1 to 2 and comparative example 1 is oral administrated; and

FIG. 2 is a schematic diagram showing sprayer for producing water-
10 insoluble drug microparticles combined with a water-soluble polymer used in the present invention.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides a pharmaceutical active ingredient
15 including water-insoluble drug. The pharmaceutical active ingredient exhibits good bioavailability. For that purpose, in the present invention, microparticles is formed by using a water-insoluble drug and water-soluble polymer without a surfactant which causes gastrointestinal tract damage.

The method of preparing pharmaceutical product for oral administrating
20 water-insoluble drug will be described in more detail.

A water-insoluble drug is dissolved in an organic solvent such as acetone to prepare a drug solution. As the water-insoluble drug, ipriflavone, biphenyl dimethyl dicarboxylate and cyclosporin may be used.

A water-soluble polymer is dissolved in an organic solvent such as

ethanol aqueous solution to prepare a polymer solution. As the water-soluble polymer, cellulose type compound may be used. The exemplary of cellulose type compound is ethylcellulose, polyethyleneglycol, carboxymethylcellulose, polyethyleneglycol, polyvinylpyrrolidone, dextran, poloxamer and a mixture
5 thereof.

The drug is mixed with the polymer in the weight ratio of 1 : 0.1 to 10, preferably 1 : 0.1 to 2. The mixed solution is spray-dried, thereby obtaining water-insoluble drug powder, microparticles combined with water-soluble polymer.

10 For obtaining microparticles, since rotary-evaporation or freeze-dry step has been used in the conventional process, the preparation is complicate, thereby requiring the specific technology. On the contrary, in the present invention, according to the performance of the spray-drying step, the preparation is simple and therefor, it is not required the specific technology.
15 The exemplary of a spray dryer used in the spray-drying step in the present invention is shown in Fig. 2. As shown in Fig.2, the mixed solution and air are injected into a spray-dryer body, while raising the ambient temperature by the heated air and mixed solution is changed from solution form to microparticle form by heated air.

20 For increasing bioavailability, the drug microparticles combined with polymer may be mixed with oil in the weight of 1 : 1 to 10. It is preferred that the drug microparticles mixed with oil because bioavailability increases. When oil amount is lower than 1, it is difficult to mix the drug micropartices with oil. On the contrary, oil amount exceeds 10, it is difficult to charge the mixture to a

capsule. As the oil, corn oil, peanut oil, coconut oil, castor oil, sesame oil, perilla oil, sunflower oil, walnut oil and cacao butter may be used.

The water-insoluble drug microparticles combined with water-soluble polymer may be used as an active ingredient for a pharmaceutical composition
5 for oral administration.

The pharmaceutical composition further includes vehicle or a disintegrant, a lubricant. In addition, the pharmaceutical composition may include other pharmaceutical excipients such as stabilizer, a preservatives, an electrolyte, etc used in the pharmaceuticals

10 The present invention is further explained in more details with reference to the following examples. The examples are not intended to limit the present invention.

Example 1

1 part by weight of ipriflavone was dissolved in 8 parts by weight of
15 acetone to prepare a water-insoluble drug solution. 2 parts by weight of hydroxypropylmethylcellulose was dissolved in an aqueous ethanol solution including 1 part by weight of water and 1 part by weight of ethanol to prepare a water-soluble polymer solution. 4 parts by weight of the polymer solution was added to 9 parts by weight of the drug solution and mixed well by using a
20 homogenizer. The mixed solution was spray-dried at 50 °C for 20 minutes by using a spray-dryer shown in Fig.2 to obtain the water-insoluble drug microparticles combined with water-soluble polymer. 3 parts by weight of the drug microparticles was mixed with 10 parts by weight of corn oil to obtain a pharmaceutical active ingredient.

Example 2

A pharmaceutical active ingredient was prepared by the same procedure in Example 1 except that corn oil was not used.

Comparative example 1

5 The commercial product of Ipriflavone was used for oral administering water-insoluble drug.

Pharmaceutical compositions of the present invention were prepared by the conventional pharmaceutical process with these pharmaceutical active ingredients of examples 1 to 2. Furthermore, pharmaceutical compositions of comparative example 1 was prepared by disintegrating 0.27 parts by weight of Ipriflavone of comparative example 1 in water. These pharmaceutical compositions was used as powder or tablets. These tablets or powder were oral administered into white rats in the amount of 50 mg of drug per kg of rat's weight with conventional method. The amounts of ipriflavone in the tablets or powder which did not absorbed in the rat's body and excreted to the out of the body were determined. The result shows in Fig. 1.

The result of comparative example 1 show that the most of ingredient ipriflavone did not absorbed in the rat's body and excreted to the out of the body were shown in Fig. 1. As shown in Fig. 1, when the pharmaceutical active ingredient including the drug microparticles and water of the Example 2 was oral administered, absorption in the body increased two times more than the Comparative example 1. Furthermore, when the pharmaceutical active ingredient including oil of example 1, absorbing in the body is seven times more than the comparative example 1.

As described above, when the drug microparticles obtained by the present invention is oral administered with oil, the increased bioavailability is exhibited. Accordingly, the drug of the present invention can be oral administered. Furthermore, it is not required for the drug to administered into a
5 patient three or four times a day rather than the conventional water-insoluble drug.

While the present invention has been described in detail with reference to the preferred embodiments, those skilled in the art will appreciate that various modifications and substitutions can be made thereto without departing from the
10 spirit and scope of the present invention as set forth in the appended claims.

WHAT IS CLAIMED IS:

1. A method of preparing a pharmaceutical active ingredient composition including water-insoluble drug for oral administration comprising the steps of:
 - 5 mixing water-insoluble drug in an organic solvent with water-soluble polymer in an aqueous solvent;
spray-drying the mixture.
 2. The method of claim 1 wherein the polymer is selected from the group consisting of ethylcellulose, polyvinylpyrrolidone, polyethyleneglycol,
10 carboxymethylcellulose, hydroxypropylmethylcellulose, dextran and poloxamer.
 3. The method of claim 1 wherein the drug is selected from the group consisting of ipriflavone, biphenyldimethyldicarboxylate and cyclosporin.
 4. The method of claim 1 wherein the weight ratio of the drug and polymer is 1 : 0.1 to 10.
 - 15 5. The method of claim 1 further comprising the step of mixing the microparticles with oil.
 6. The method of claim 1 wherein the oil is selected from the group consisting of corn oil, peanut oil, coconut oil, castor oil, sesame oil, perilla oil, sunflower oil, walnut oil and cacao butter.
 - 20 7. The method of claim 5 wherein the weight ratio of the microparticles and oil is 1 : 1 to 10.
 8. A pharmaceutical composition for oral administration, comprising a pharmaceutical active ingredient water-insoluble drug microparticles combined with water-soluble polymer.

9. The pharmaceutical composition of claim 8 wherein the drug is selected from the group consisting of ipriflavone, biphenyldimethyldicarboxylate and cyclosporin.

10. The pharmaceutical composition of claim 8 wherein the polymer
5 is selected from the group consisting of ethylcellulose, polyvinylpyrrolidone, polyethyleneglycol, carboxymethylcellulose, hydroxypropylmethylcellulose, dextran and poloxomer.

FIG.1

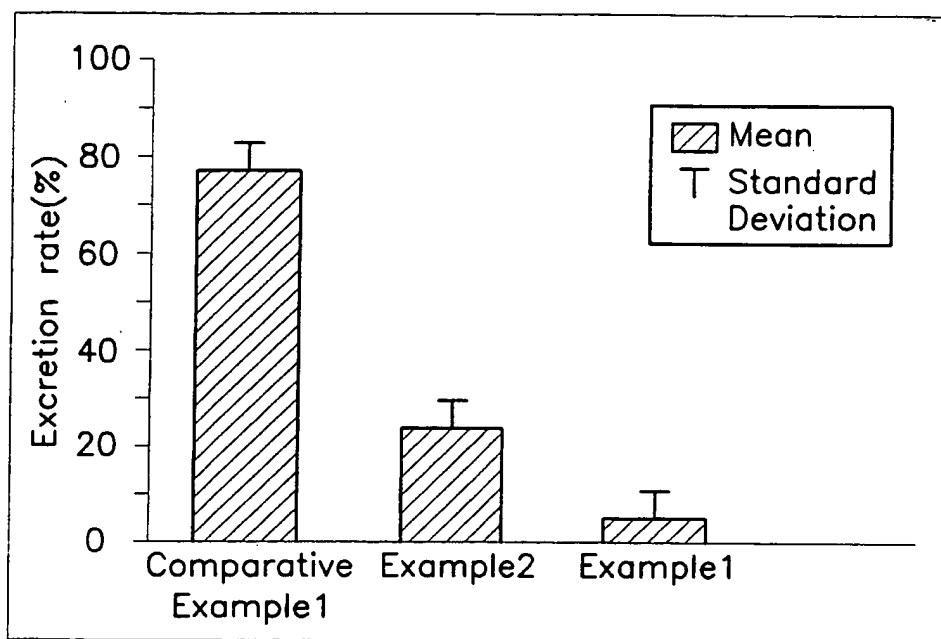
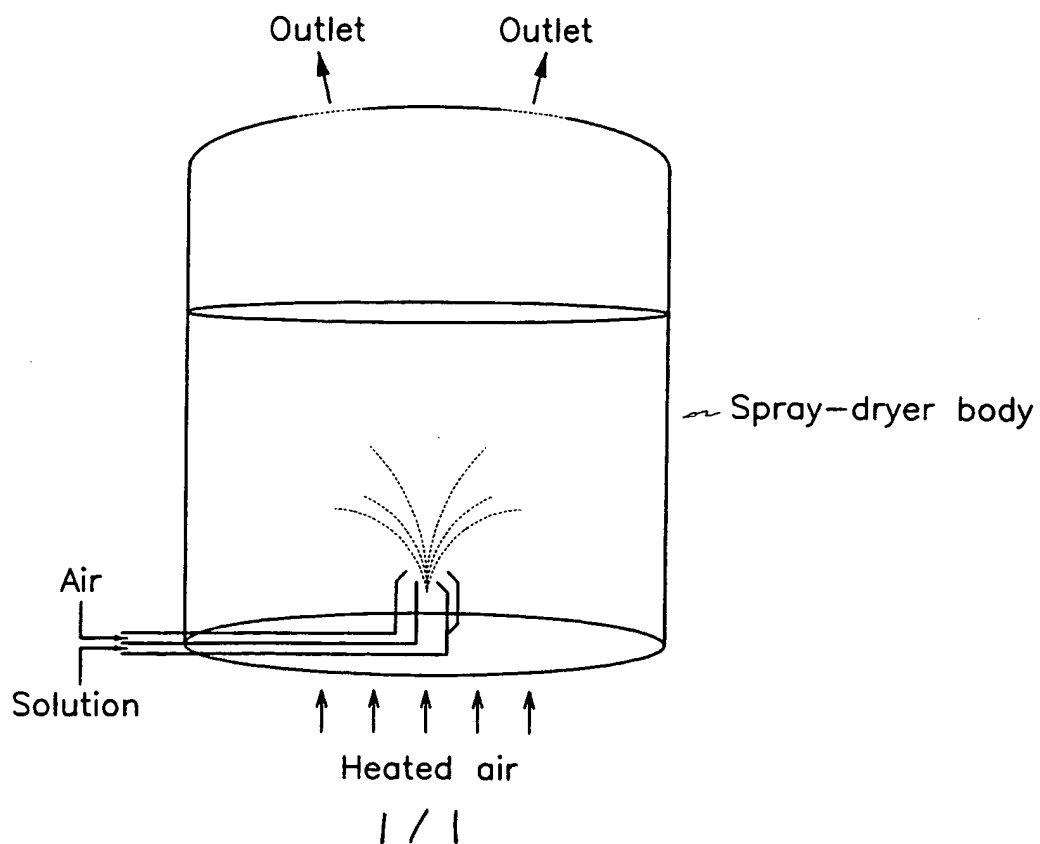


FIG.2



INTERNATIONAL SEARCH REPORT

International application No.
PCT/KR 99/00025

A. CLASSIFICATION OF SUBJECT MATTER

IPC⁷: A 61 K 9/14, A 61 K 47/44, A 61 K 38/13, A 61 K 47/30

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC⁷: A 61 K, C 08 L

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

WPI, TXTE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 670 166 A2 (ELI LILLY COMPANY) 06 September 1995 (06.09.95), abstract; page 5, lines 2-10; claims 1, 2, 5, 8.	1-10
X	WO 95/32726 A (YUHAN CORPORATION) 07 December 1995 (07.12.95), abstract; page 4, lines 15-25; claims.	1-4, 8-10
X	US 5 817 343 A (BURKE) 06 October 1998 (06.10.98), abstract; column 6, lines 63.67; column 7, lines 1-15, 40-45; claims 1, 31, 33.	1,2,8,10
X	EP 0 012 496 A1 (BEECHAM GROUP LIMITED) 25 June 1980 (26.06.80), abstract; page 3, lines 1-16; page 4, lines 18-21; page 5, lines 1-12.	1,2,4,8

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents: „A“ document defining the general state of the art which is not considered to be of particular relevance „E“ earlier application or patent but published on or after the international filing date „L“ document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) „O“ document referring to an oral disclosure, use, exhibition or other means „P“ document published prior to the international filing date but later than the priority date claimed	„T“ later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention „X“ document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone „Y“ document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art „&“ document member of the same patent family
--	--

Date of the actual completion of the international search 14 October 1999 (14.10.99)	Date of mailing of the international search report 08 November 1999 (08.11.99)
Name and mailing address of the ISA/AT Austrian Patent Office Kohlmarkt 8-10; A-1014 Vienna Facsimile No. 1/53424/200	Authorized officer Krenn Telephone No. 1/53424/435

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/KR 99/00025

In Recherchenbericht angeführtes Patentdokument Patent document cited in search report Document de brevet cité dans le rapport de recherche	Datum der Veröffentlichung Publication date Date de publication	Mitglied(er) der Patentfamilie Patent family member(s) Membre(s) de la famille de brevets	Datum der Veröffentlichung Publication date Date de publication
EP A2 670166	06-09-1995	AU A1 13544/95 BR A 9500754 CA AA 2138607 CN A 1114588 CZ A3 9500519 EP A3 670166 HU A0 9500618 HU A2 75252 IL A0 112745 JP A2 8040936 NO A0 950134 ND A 950134 NZ A 270145 PL A1 307469 ZA A 9500936	07-09-1995 24-10-1995 02-09-1995 10-01-1996 18-10-1995 12-06-1996 28-04-1996 28-05-1997 26-05-1995 13-02-1996 13-01-1996 04-09-1996 27-08-1996 04-09-1996 09-10-1995
WO A1 9532726		keine - none - rien	
US A 5817343	06-10-1998	AU A1 27517/97 CA AA 2253667 EP A1 914095 WO A1 9742940	05-12-1997 20-11-1997 12-05-1999 20-11-1997
EP A1 12496	25-06-1980	AU A1 52284/79 AU B2 531634 DE C0 2965917 EP B1 12496 JP A2 55075387 NZ A 191982 US A 4316886	12-06-1980 01-09-1983 25-08-1983 20-07-1983 14-06-1980 23-11-1982 23-02-1982